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LETTER TO THE EDITOR

Reply: Neural detection of complex sound sequences or of statistical regularities in the absence of consciousness?

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Sir,

We read with interest the letter by Naccache and colleagues (2015) on our recent paper showing unconscious processing of global auditory regularities. We thank the Editor for the opportunity to provide further details about our results especially in the context of a growing interest around the interpretation of the global effect in disorders of consciousness (Piarulli *et al.*, 2015) and in sleep research (Strauss *et al.*, 2015).

Naccache and colleagues questioned the reliability of the conclusion of our paper arguing that previous studies have never shown a global effect unless healthy controls/patients were aware of the global regularity violation. In this context, they propose a different interpretation of our study along three lines: (i) the observed effect is not 'global' because it does not have the characteristic features previously reported in the literature in terms of latency (> 300 ms) and associated EEG component (i.e. P300) both in controls and in patients; (ii) the reported effect might be driven by violation detection between two consecutive sounds and not at the level of groups of sounds as required by a true global discrimination; and (iii) comatose patients showing the global effect were in fact conscious.

Global effect in healthy controls

In response to the first point, we should first clarify that the latencies of the observed global effect in control subjects are indeed in accordance with what was reported previously in the literature (i.e. Fig. 4 in Bekinschtein *et al.*, 2009) as all subjects exhibited discriminative periods after 300 ms post-stimulus onset (Fig. 1). We have never reported that the global discrimination '... occurred during the early time period (0–250 ms) following the onset of the irregular sound' as claimed in the letter. In our study the 0–250 ms time periods were the result of the topographic consistency test (Koenig and Melie-García, 2010), which quantifies the presence of an evoked response to the sounds independently of the auditory discrimination analysis and therefore of the global effect (Supplementary material in Tzovara *et al.*, 2015). Also, in accordance with previous literature (Bekinschtein *et al.*, 2009; King *et al.*, 2013), we have shown that active controls outperform the passive listeners both in terms of decoding performance and number of individuals with significant global discrimination (Tzovara *et al.*, 2015). Nevertheless, as Naccache and

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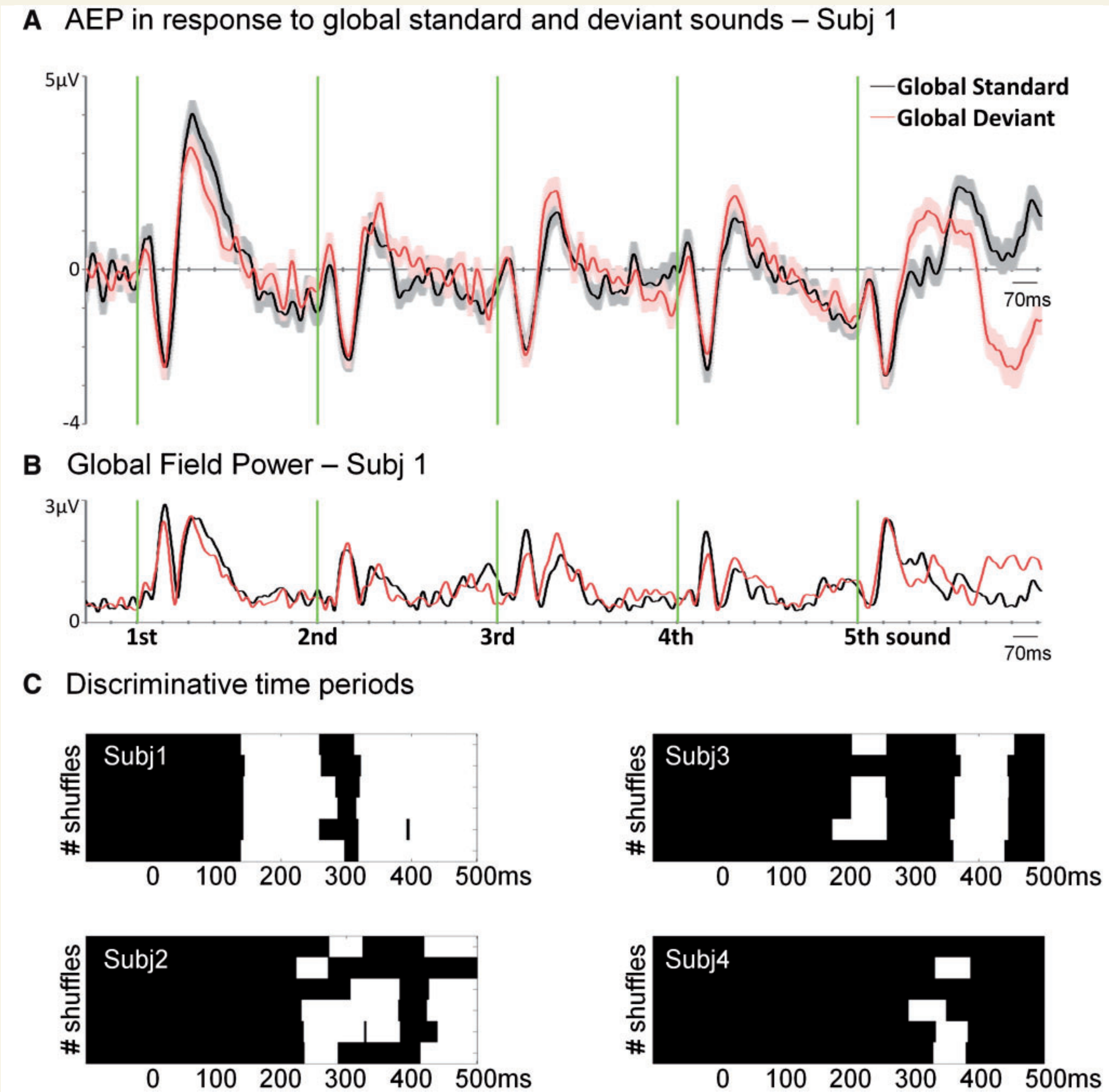

Figure 1 Auditory evoked potentials and discriminative time periods in active controls. (**A** and **B**) Exemplar auditory evoked potentials (AEPs) recorded at the Cz electrode and global field power in response to global standard and global deviant sequence of five sounds. The detection of the global regularity in this active control manifests as a sustained difference in the response to the global violation as shown by both the auditory evoked potential and global field power representations. (**C**) A summary of the discriminative periods in response to global standards and global deviants, as revealed by the decoding analysis of the four active subjects with significant results. Each horizontal line displays the discriminative periods revealed by the decoding algorithm in each of the six shuffles in the data set. The onset (time 0) refers to the beginning of the fifth sound of the group of five. All subjects exhibited at least one discriminative time period after 300 ms post-stimulus onset. The waveforms plotted in **A** and **B** correspond to the first subject of **C** (Subj 1).

colleagues pointed out, the total number of subjects with a significant decoding result is lower compared to previous studies (King *et al.*, 2013). Several reasons can explain this discrepancy. First, we tested the global effect in a relatively old cohort of subjects, age-matched to the coma patients (i.e. mean age: 62 ± 2 years for the passive and 56 ± 2 for the active group) differently to previous studies that included only young controls—i.e. mean age: 27 ± 3 years in Bekinschtein *et al.* (2009) and 23 ± 1 or 25 ± 5 years in King *et al.* (2013). Second, in our study we implemented a global paradigm based on changes in the sounds' duration while all previous studies have been based on changes in pitch. The perceptual detection of duration deviants is more challenging compared to pitch deviants, providing in our study an accuracy of perceptual detection ranging between 55 and 92% in active controls. Third, the significance of our decoding results is based on a strict statistical criterion entailing a comparison between the true decoding performance and the distribution of the values obtained after reshuffling the data 500 times. Previous studies were either based on univariate statistics at the single electrode level (for example as reported in Bekinschtein *et al*., 2009 or Faugeras *et al*., 2011), or on decoding results statistically assessed at the group level, without within-subject permutations (King *et al*., 2013).

Global effect in comatose patients

To our knowledge, our study was the first to explore global auditory discrimination in post-anoxic patients treated with therapeutic hypothermia and pharmacological sedation; therefore, our data cannot be readily compared to results obtained in vegetative and minimally conscious patients (King *et al*., 2013) in terms of latencies and associated stereotypical waveforms. Nevertheless, as in this previous study, we did control whether the global discrimination was driven by a somehow trivial violation detection at the level of two adjacent sounds and typically eliciting a mismatch negativity response (MMN). Indeed, we have shown that the global effect in comatose patients persisted in the unfavourable context where global deviant sounds did not correspond to local deviant ones (Supplementary material in Tzovara *et al*., 2015). This control analysis suggests that the global discrimination was not trivially driven by an MMN modulation. We therefore do not believe that our results may correspond to an unconscious modulation of the early MMN by the statistical regularities, but that they reflect detection of global regularities, previously associated only with a classic P3b component, observed during conscious access to the auditory stimuli.

Consciousness level assessment in patients

The patients included in the present study were all treated with mild therapeutic hypothermia and analgo-sedation: they were thus not only in coma following cardiac arrest but also under midazolam at sedative doses (i.e. 0.1 mg/kg/h). To provide a clinical parallel, similar doses are commonly used also to treat patients in status epilepticus, where coma induction is part of the therapeutic armamentarium (Rossetti and Lowenstein, 2011). Naccache and colleagues correctly mention that curarisation is used during therapeutic hypothermia, but this is only intermittent and occurs only to counteract marked shivering (Oddo and Rossetti, 2014), therefore allowing—together with the clinical EEG—a periodic assessment of the state of patients; moreover it is never administered after return to normal temperature. Under such conditions, all clinical evidence was in accordance with a complete absence of any sign of arousal, a necessary condition for conscious processing (Laureys *et al*., 2004). The complete absence of arousal was inferred with the Sedation-Agitation and Coma Glasgow Scale that provided the lowest scores at least during hypothermia (see Table 1 in Tzovara *et al*., 2015). Our patients were intubated, with eyes closed, and not arousable by potent painful stimuli, fulfilling the definition of coma (Laureys *et al*., 2004). On the basis of this clinical evidence, one can conclude that the patients included in the study were indeed unconscious, at least during hypothermia.

In summary, we believe that our experimental evidence strongly supports the existence of an automatic mechanism for global regularity detection, which is modulated by task demands. This mechanism appears preserved even in the absence of any conscious perception of the stimuli, and irrespective of an MMN response.

Previous literature has mainly focused on patients in a reduced consciousness state for a prolonged period of time (Bekinschtein *et al*., 2009; Faugeras *et al*., 2011; King *et al*., 2013), when general neural functions have likely deteriorated (Tzovara *et al*., 2013). We speculate that previous studies may have been looking at the tail of an ongoing process (Piarulli *et al*., 2015), and at a point where a global effect is no longer present.

We would like to finish this letter by thanking Naccache and colleagues for stimulating a scientific discussion that may enhance the understanding of cerebral processes during consciousness impairment, and renew our proposal to them to directly compare our two versions of the global paradigms on the same patients, in early coma and chronic stage.

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References

Bekinschtein TA, Dehaene S, Rohaut B, Tadel F, Cohen L, Naccache L. Neural signature of the conscious processing of auditory regularities. Proc Natl Acad Sci USA 2009; 106: 1672–7.

Faugeras F, Rohaut B, Weiss N, Bekinschtein TA, Galanaud D, Puybasset L, et al. Probing consciousness with event-related potentials in the vegetative state. Neurology 2011; 77: 264–8.

King JR, Faugeras F, Gramfort A, Schurger A, El Karoui I, Sitt JD, et al. Single-trial decoding of auditory novelty responses facilitates the detection of residual consciousness. Neuroimage 2013; 83: 726–38.

Koenig T, Melie-García L. A method to determine the presence of averaged event-related fields using randomization tests. Brain Topogr 2010; 23: 233–42.

Laureys S, Owen AM, Schiff ND. Brain functin in coma, vegetative state, and related disorders. Lancet 2004; 3: 537–46.

Naccache L, King J-R, Sitt J, Engemann D, El Karoui I, Rohaut B et al. Neural detection of complex sound sequences or of statistical regularities in the absence of consciousness? Brain 2015; in press.

Oddo M, Rossetti AO. Early multimodal outcome prediction after cardiac arrest in patients treated with hypothermia. Crit Care Med 2014; 42: 1340–7.

Piarulli A, Charland-Verville V, Laureys S. Neural detection of complex sound sequences in the absence of consciousness. Brain 2015; 138: 1129–37.

Rossetti AO, Lowenstein DH. Management of refractory status epilepticus in adults: Still more questions than answers. Lancet Neurol 2011; 10: 922–30.

Strauss M, Sitt JD, King J-R, Elbaz M, Azizi L, Buiatti M, et al. Disruption of hierarchical predictive coding during sleep. Proc Natl Acad Sci 2015; 12: E1353–62.

Tzovara A, Rossetti AO, Spierer L, Grivel J, Murray MM, Oddo M, et al. Progression of auditory discrimination based on neural decoding predicts awakening from coma. Brain 2013; 136: 81–9.

Tzovara A, Simonin A, Oddo M, Rossetti AO, De Lucia M. Neural detection of complex sound sequences in the absence of consciousness. Brain 2015; 138: 1160–6.